REMARKS

Support for the amendments

The amendment to the specification reconciles the § 120 priority claim with the filing papers and § 1.63 declaration in this application and updates the status for the other listed applications. The title and abstract are revised to correspond to the claimed subject matter.

The amendment to claim 21 is supported by original Figures 4 and 5 and the disclosure generally. The figures as filed identify the predicted signal peptide cleavage sites as recited in the amended claims. The disclosure as filed conveys to the skilled worker that cleavage of the propeptides as indicated is expected in the expression systems of the invention. The amended claim recites the portions of SEQ ID NOs: 4 and 6 corresponding to positions +1 to +107 of the light chain variable region and positions +1 to +113 of the heavy chain variable region as shown in Figures 4 and 5, respectively.

The recitation of "pharmaceutical carrier" and "pharmaceutically acceptable buffer" in amended claims 41 and 42 and new claims 69 and 70 is supported, *e.g.*, at page 14, paragraph bridging to 15. Express support for "non-marrow ablative" in amended claim 57 is found, *e.g.*, at page 18, line 7. New claims 67-70 are supported by the disclosure generally, *e.g.*, at the paragraph bridging pages 13-14. New claims 71 and 72 are supported by the disclosure as filed, *e.g.*, at page 12, lines 8-10, and page 21, lines 14-17, respectively.

Claims 22-25, 27, 28, 33-40, 44, 49, 50, and 63-67 are canceled solely to expedite prosecution, without disclaimer or prejudice to their presentation in a related or continuing application. Similarly, the claim amendments discussed with particularity below are presented solely to expedite prosecution, without disclaimer or prejudice to the later prosecution of the subject matter of the amended claims as they stood prior to this amendment.

Various claim amendments address matters of form and maintain consonance of dependent claims with amended base claims. The claims are also amended by way of correction of Figure 4 and the corresponding sequence listing, as discussed below.

The amendments at pages 16 and 26 correct obvious informalities and identify trademarked names.

The amendments add no new matter to the disclosure.

Drawing correction

A substitute sheet for Figure 5 is attached. The correction involves the rectification of a typographical error in the amino acid sequence of the heavy chain variable domain of chimeric antibody C2B8. In particular, the predicted translation is corrected to indicate that the residue at position +14 is Pro, not Ala.

The nucleotide sequence in the figure as filed is correct. The codon corresponding to position +14 (CCT) in fact encodes the amino acid proline (Pro), not alanine (Ala) as shown in the figure. This is evidenced by the attached table showing the amino acids encoded by DNA codons, copied from the textbook by Lodish *et al.*, *Molecular Cell Biology*, available online at the PubMed website at the U.S. National Library of Medicine. (Note that this table lists U instead of T, reflecting the codons employed in RNA sequences.)

The correction is supported by the present application as filed and by the evidence in the priority applications. The following evidence supports the correctness of the nucleotide sequence and the assignment of residue +14 of the heavy chain at Pro instead of Ala.

- First, Figure 3, which provides the complete nucleotide sequence of the TCAE-8 vector, shows the same nucleotide sequence as Figure 5 in the region of interest. A copy of the relevant part of that figure from U.S. Patent No. 5,736,137 with the CCT codon boxed is attached.

- Second, the nucleotide sequence shown in the original sequence listing as SEQ ID NO: 3 (now SEQ ID NO: 5 in this application) is correct. The sequence listing was present in the application as filed.

- Third, the corresponding Fig. 5 from the original application in this series, U.S. application serial no. 07/978,891, shows the same nucleotide sequence and the correct predicted amino acid sequence (*i.e.*, including a Pro residue at position +14). A copy of that figure indicating residue +14 is also attached.

- Finally, the undersigned states that he has reviewed information, believed to be correct, indicating that the nucleotide sequence in the deposited clone, ATCC 69119, does in fact encode a Pro residue at position +14 of the heavy chain.

The error in Figure 5 of the application as filed is an "obvious error" that can be properly corrected on the evidence of record. Because the CCT codon always encodes a Pro amino acid residue, the skilled worker would immediately recognize that an error was present. Importantly, the skilled worker would also immediately understand what the correction must be. Also, the evidence in the patent application and in the priority document fully supports correcting the figure to show a Pro residue at position +14 in the amino acid sequence.

Corrected sequence listing

A substitute sequence listing accompanies this reply. The sequence listing is revised to reflect the correction to the amino acid sequence shown in Figure 5 (SEQ ID NO: 6) as discussed immediately above. Except for this correction, the sequences in the new sequence listing are identical to the sequences in the application as filed. For the reasons discussed in connection with the correction of the figure, applicant submits that this amendment adds no new matter.

A computer-readable copy of the attached sequence listing is filed with this reply on compact disc. In compliance with 37 C.F.R. § 1.821(e), the undersigned states that the paper and computer-readable copies of the sequence listing are identical.

Informalities

In response to the examiner's observation at ¶ 3 of the Office action, an information disclosure statement citing WO 94/11026, including a copy of the cited document, accompanies this reply.

The informality regarding the priority claim, as noted by the examiner in the last Office action at ¶ 4, has been rectified by amendment as set forth above.

Rejections under 35 U.S.C. § 112, first paragraph

At ¶ 8 of the Office action, all of previously pending claims 21-67 are rejected on various grounds under the written description requirement of § 112, first paragraph. Applicant respectfully traverses these rejections.

Point A

Claims 21-25 are rejected for failing to recite "immunologically active." Applicant does not agree that the disclosure is limited to a description of such antibodies. The disclosure describes antibodies for imaging, such as the murine antibody 2B8. One skilled in the art would appreciate that such antibodies would be effective for the purposes described, whether or not they were immunologically active. In any case, claims 21-25 have been amended to recite "immunologically active," and this ground of rejection as stated in the Office action is accordingly moot.

Claims 21-25 are also rejected because they are said to read on antibodies comprising more than one heavy and one light chain. Applicant notes that the written description as filed provides express support for antibodies comprising two light chains and two heavy chains, *e.g.*, at page 11, line 16. Moreover, the claims do not affirmatively recite a plurality of different light chains or heavy chains. The specification describes and enables a variety of antibodies combining the recited structural elements. The exemplary chimeric antibody, C2B8, is but one such combination. Claim 21 properly claims the combination of the heavy and light chain variable domain sequences of C2B8 in generic terms that are consonant with the disclosure as filed.

Point B

Claims 22-25 are rejected because they are said to read on multichain antibodies (22-25; point B). To expedite prosecution, applicant has canceled claims 22-25, and the rejections are therefore moot as to those claims. However, the disclosure as a whole does not fairly teach that the two chains of C2B8 must always be employed in the same antibody. The specification teaches that the TCAE-8 vector was constructed for the purpose of facilitating the coexpression of *different* heavy and light chain variable domain inserts, thus to enable the rapid production and

evaluation of a variety of antibodies. It also teaches that the component Ig chains may be separately expressed or co-expressed using separate vectors in the same cell or in different cells. *See, e.g.*, page 19, lines 22-27. Applicant submits that the description of such systems and methods for making antibodies is evidence that the heavy and light chains of C2B8 are not disclosed to be a necessary pairing.

Point C

Claims 41 and 42 are rejected because the terms "pharmaceutical composition," "imaging composition," and "pharmaceutically acceptable carrier" are said not to be recited *verbatim* in the application as filed. Claim 41 has been amended to recite a "composition" generic to both "pharmaceutical" and "imaging" uses. Applicant notes that the specification fully describes such uses for the compositions of the invention.

Claims 41 and 42 have been amended to recite "pharmaceutical carrier" and "pharmaceutically acceptable buffer," terms having express support in the disclosure as filed, as indicated above. Applicant notes that at the paragraph bridging pages 14-15 of the specification, the reference work, Remington's *Pharmaceutical Carriers & Formulations*, is cited for its description of "[m]ethods for preparing parenterally administerable agents" and is incorporated by reference. In respect of the examiner's concern that the claim terms may encompass carrier components other than buffers, applicant notes that Remington's is recognized in the art for its encyclopedic description of components employed in pharmaceutical formulations. As this work forms a part of the disclosure as filed, applicant believes that this concern is not properly based.

The examiner states that claims 43 and 44 did not affirmatively require that the radiolabel be attached to the claimed antibody. Claim 43 has been amended to state that the recited radiolabel is attached to the antibody of the claim.

Applicant notes that the dosages recited in claims 52 and 54 find express support at least at page 15, line 8, and page 17, line 25, respectively. Non-myeloablative dosages for radiolabeled antibodies are described at the first full paragraph on page 18. To expedite prosecution, claim 57 has been amended to use the term "non-marrow ablative," as recited at page 18, line 7.

Point D

Claims 58, 59, 63, and 64 are rejected on the ground that they would read on antibodies comprising constant regions from species other than human (point D). Applicant notes that the written description as filed contemplates antibodies containing sequence components from a wide variety of animal sources. *See* the specification at the paragraph bridging pages 12-13. Thus, applicant does not agree with the examiner's characterization of the disclosure.

Claim 58 and the claims that depend from it do not require any of the limitations that the examiner notes, such as a camel constant region. Moreover, claim 58 is properly drawn in view of the disclosure as filed to encompass both 2B8 and C2B8. Thus, antibodies "with a heavy or light chain other than that found in 2B8" are not only described, but exemplified. Applicant believes that this ground of rejection is not well taken.

Rejections under § 102(b)

At ¶ 11 of the outstanding action, the Office rejects all of the claims under 35 U.S.C. § 102(b) over U.S. Patent No. 5,736,137. The Office's reasoning is that because several limitations in the claims are alleged to be new matter, claims 21-67 are entitled to only the filing date of this application.

For the reasons set forth above in traversal of the rejections under § 112, applicant maintains that all of the pending claims are fully supported in each of the applications to which this application claims priority. Accordingly, the claims are entitled to the benefit of the filing date of application serial no. 07/978,891, filed November 13, 1992, and the cited reference is not available as prior art against the pending claims. Thus, the rejection under § 102(b) is not properly based and should be withdrawn.

Double patenting

Applicant acknowledges the nonstatutory double patenting rejection of claims 21-58 and 63 over claims in U.S. Patent No. 5,736,137. Applicant agrees to file a terminal disclaimer over the '137 patent when the other substantive patentability issues are resolved, provided the claims in this application are in substantially the same form as the current claims at that time.

Conclusion

Applicant believes that this reply fully and properly responds to the outstanding Office action. Withdrawal of the stated rejections and allowance of claims 21, 26, 29-32, 41-43, 45-48, 51-62, and 68-72 are respectfully requested.

Respectfully submitted,

David L. Fitzgerald, Reg. No. 47,347
Attorney for Biogen Idec Inc.

12 August 2005

SIDLEY AUSTIN BROWN & WOOD LLP
1501 K Street, N.W.
Washington, DC 20005

tel. (202) 736-8818
fax (202) 736-8711

Table 4-2. The Genetic Code (RNA to Amino Acids)*

First Position (5′ end)	Second Position				Third Position (3′ end)
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop (och)	Stop	A
	Leu	Ser	Stop (amb)	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu (Met)	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met (start)	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val (Met)	Ala	Glu	Gly	G

*"Stop (och)" stands for the ochre termination triplet, and "Stop (amb)" for the amber, named after the bacterial strains in which they were identi-

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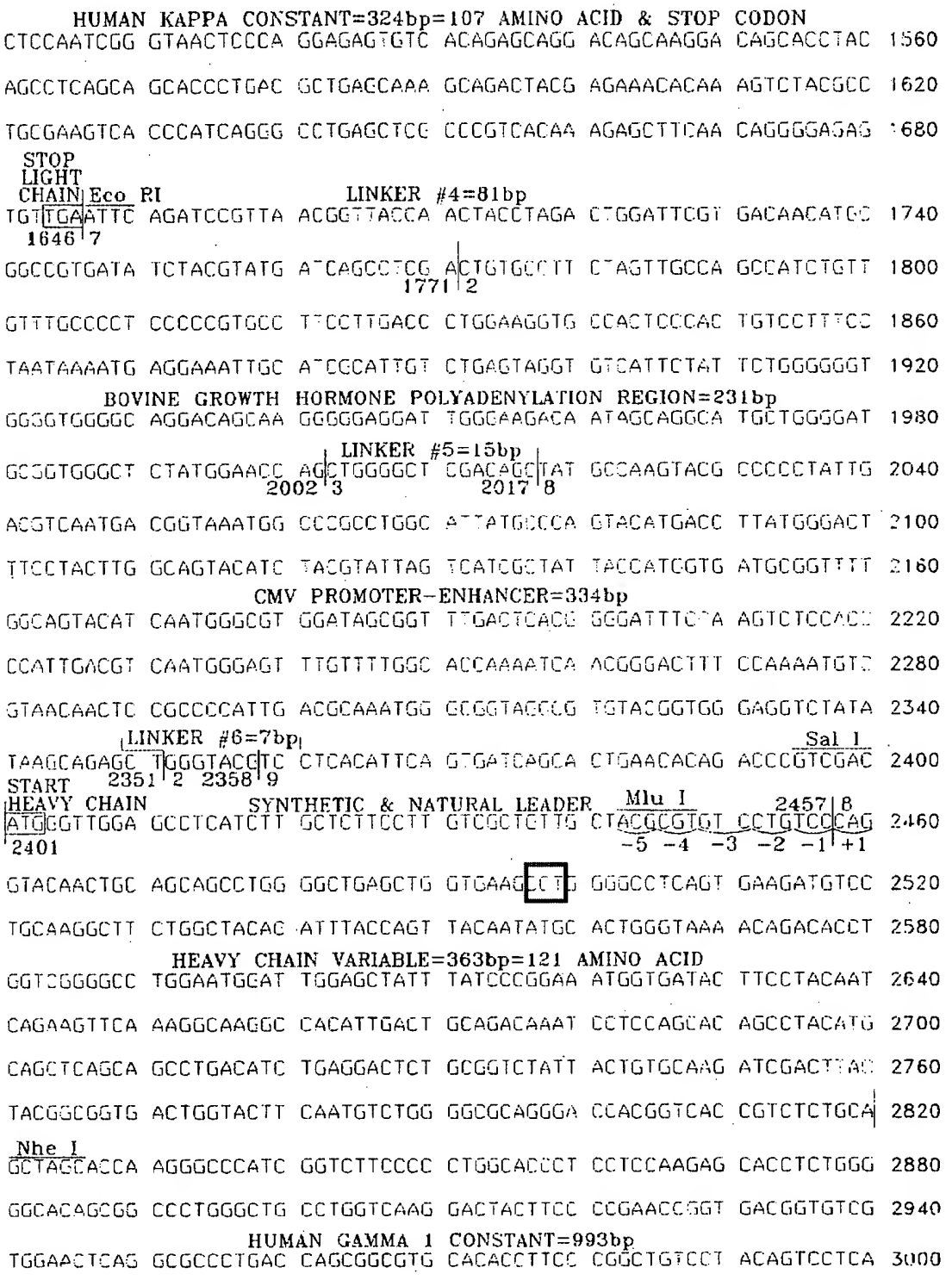

FIG. 3B

ANNOTATED SHEET

07 978891

mHvy

FIGURE 5

Leader

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          -19             -15             -10              -5
Frame 1   Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg Val
          ATG GGT TGG AGC CTC ATC TTG CTC TTC CTT GTC GCT GTT GCT ACG CGT GTC
                2409        2418        2427        2436        2445

      -1| +1      FR1                            10                  15
Leu Ser| Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser
CTG TCC| CAG GTA CAA CTG CAG CAG CCT GGG GCT GAG CTG GTG AAG CCT GGG GCC TCA
       2460        2469        2478        2487        2496        2505

          20                  25                  30| 31   CDR1      35 |36
Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr |Ser Tyr Asn Met His |Trp
GTG AAG ATG TCC TGC AAG GCT TCT GGC TAC ACA TTT ACC |AGT TAC AAT ATG CAC |TGG
       2517        2526        2535        2544    |   2553        2562 |

             40 FR2             45              49 |50      52 52A  53  54
Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly |Ala Ile Tyr Pro Gly Asn
GTA AAA CAG ACA CCT GGT CGG GGC CTG GAA TGG ATT GGA |GCT ATT TAT CCC GGA AAT
       2574        2583        2592        2601    |   2610        2619

55          CDR2     60                  65 |66  FR3          70
Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly |Lys Ala Thr Leu Thr Ala Asp Lys
GGT GAT ACT TCC TAC AAT CAG AAG TTC AAA GGC |AAG GCC ACA TTG ACT GCA GAC AAA
       2631        2640        2649        2658        2667        2676

   75                  80      82  82A 82B 82C 83      85
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
TCC TCC AGC ACA GCC TAC ATG CAG CTC AGC AGC CTG ACA TCT GAG GAC TCT GCG GTC
       2688        2697        2706        2715        2724        2733

90              94| 95      CDR3       100 100A 100B 100C 100D 101 |102 103
Tyr Tyr Cys Ala Arg| Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val |Trp Gly
TAT TAC TGT GCA AGA| TCG ACT TAC TAC GGC GGT GAC TGG TAC TTC AAT GTC |TGG GGC
       2745        2754        2763        2772        2781        2790

105 FR4          110         113
Ala Gly Thr Thr Val Thr Val Ser Ala
GCA GGG ACC ACG GTC ACC GTC TCT GCA
       2802        2811        2820
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